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### Search Results -

Terms	Documents
pulmonary adj5 (microparticle or microsphere)	37

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**Search:**

L1

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Recall Text

Clear

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DATE: Thursday, March 03, 2005 [Printable Copy](#) [Create Case](#)

Set Name Query  
side by side

Hit Count Set Name  
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L1 pulmonary adj5 (microparticle or microsphere) 37 L1

END OF SEARCH HISTORY

[First Hit](#) [Fwd Refs](#)[Previous Doc](#) [Next Doc](#) [Go to Doc#](#) [Generate Collection](#) [Print](#)

L1: Entry 43 of 80

File: USPT

Feb 27, 2001

DOCUMENT-IDENTIFIER: US 6193954 B1

\*\* See image for Certificate of Correction \*\*

TITLE: Formulations for pulmonary delivery of dopamine agonists

Brief Summary Text (13):

In addition to delivery via metered dose inhalers, other pulmonary delivery systems include powders, microparticles and aqueous and non-aqueous based solutions or dispersions which are administered through and/or into the airways by nasal or trachael routes.

[Previous Doc](#) [Next Doc](#) [Go to Doc#](#)

[First Hit](#) [Fwd Refs](#)[Previous Doc](#) [Next Doc](#) [Go to Doc#](#) [Generate Collection](#) [Print](#)

L1: Entry 56 of 80

File: USPT

Dec 7, 1999

DOCUMENT-IDENTIFIER: US 5997848 A

TITLE: Methods and compositions for pulmonary delivery of insulin

Brief Summary Text (3):

The present invention relates generally to methods and compositions for the respiratory delivery of insulin to diabetic patients. More particularly, the present invention relates to the pulmonary delivery of dry powder insulin preparations for rapid systemic absorption through the lungs.

Brief Summary Text (11):

The respiratory delivery of aerosolized aqueous insulin solutions is described in a number of references, beginning with Gansslen (1925) Klin. Wochenschr. 4:71 and including Laube et al. (1993) JAMA 269:2106-21-9; Elliott et al. (1987) Aust. Paediatr. J. 23:293-297; Wigley et al. (1971) Diabetes 20:552-556. Corthorpe et al. (1992) Pharm Res 9:764-768; Govinda (1959) Indian J. Physiol. Pharmacol. 3:161-167; Hastings et al. (1992) J. Appl. Physiol. 73:1310-1316; Liu et al. (1993) JAMA 269:2106-2109; Nagano et al. (1985) Jikeikai Med. J. 32:503-506; Sakr (1992) Int. J. Phar. 86:1-7; and Yoshida et al. (1987) Clin. Res. 35:160-166. Pulmonary delivery of dry powder medicaments, such as insulin, in a large particle carrier vehicle is described in U.S. Pat. No. 5,254,330. A metered dose inhaler (MDI) for delivering crystalline insulin suspended in a propellant is described in Lee and Sciara (1976) J. Pharm. Sci. 65:567-572. A MDI for delivering insulin into a spacer for regulating inhalation flow rate is described in U.S. Pat. No. 5,320,094. The intrabronchial administration of recombinant insulin is briefly described in Schluter et al. (Abstract) (1984) Diabetes 33:75A and Kuhler et al. (1987) Atemw. Lungenkrkh. 13:230-232. Intranasal and respiratory delivery of a variety of polypeptides, including insulin, in the presence of an enhancer, are described in U.S. Pat. No. 5,011,678 and Nagai et al. (1984) J. Contr. Rel. 1:15-22. Intranasal delivery of insulin in the presence of enhancers and/or contained in controlled release formulations are described in U.S. Pat. Nos. 5,204,108; 4,294,829; and 4,153,689; PCT Applications WO 93/02712, WO 91/02545, WO 90/09780, and WO 88/04556; British Patent 1,527,605; Ryden and Edman (1992) Int. J. Pharm. 83:1-10; and Bjork and Edman (1988) Int. J. Pharm. 47:233-238. The preparation and stability of amorphous insulin were described by Rigsbee and Pikal at the American Association of Pharmaceutical Sciences (AAPS), Nov. 14-18, 1993, Lake Buena Vista, Fla. Methods for spray drying polypeptide, polynucleotide and other labile drugs in a carrier which forms an amorphous structure which stabilize the drug are described in European patent application 520 748.

Brief Summary Text (13):

According to the present invention, methods and compositions for the aerosolization and systemic delivery of insulin to a mammalian host, particularly a human patient suffering from diabetes, provide for rapid absorption into blood circulation while avoiding subcutaneous injection. In particular, the methods of the present invention rely on pulmonary delivery of insulin in the form of a dry powder. Surprisingly, it has been found that inhaled dry insulin powders are deposited in the alveolar regions of the lung and rapidly absorbed through the epithelial cells of the alveolar region into blood circulation. Thus, pulmonary delivery of insulin powders can be an effective alternative to administration by subcutaneous injection.

[Previous Doc](#)

[Next Doc](#)

[Go to Doc#](#)

[First Hit](#) [Fwd Refs](#)[Previous Doc](#) [Next Doc](#) [Go to Doc#](#) [Generate Collection](#) [Print](#)

L1: Entry 62 of 80

File: USPT

Jan 5, 1999

US-PAT-NO: 5855913

DOCUMENT-IDENTIFIER: US 5855913 A

TITLE: Particles incorporating surfactants for pulmonary drug delivery

DATE-ISSUED: January 5, 1999

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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Evora; Carmen	La Laguna			ES
Langer; Robert	Newton	MA		

US-CL-CURRENT: [424/489](#); [424/43](#), [424/434](#), [424/45](#), [424/46](#), [424/499](#), [424/501](#), [424/502](#)

## CLAIMS:

What is claimed is:

1. A particulate composition for drug delivery to the pulmonary system comprising:

biodegradable particles incorporating a therapeutic, prophylactic or diagnostic agent and a surfactant, wherein the particles have a tap density less than 0.4 g/cm.<sup>3</sup> and a mean diameter between 5 .mu.m and 30 .mu.m effective to yield an aerodynamic diameter of the particles of between approximately one and three microns.

2. The system of claim 1 wherein at least 50% of the particles have a mass mean diameter between 5 .mu.m and 30 .mu.m.

3. The composition of claim 1 wherein at least 50% of the particles have a mean diameter between 5 .mu.m and 15 .mu.m and a tap density less than 0.1 g/cm.<sup>3</sup>

4. The composition of claim 1 further comprising a pharmaceutically acceptable carrier for administration to the lungs.

5. The composition of claim 1 wherein the particles comprise a biodegradable polymer.

6. The composition of claim 1 wherein the particles comprise a polyester.

7. The composition of claim 1 wherein the particles comprise an excipient or a fatty acid.

8. The composition of claim 1 wherein the particles have an irregular surface structure.

9. The composition of claim 1 wherein the surfactant is coated on the surface of the particle.

10. The composition of claim 1 wherein the surfactant is incorporated within and on the surface of the particle.

11. The composition of claim 1 wherein the therapeutic agent is selected from the group consisting of proteins, polysaccharides, lipids, nucleic acids and combinations thereof.

12. The composition of claim 1 wherein the therapeutic agent is selected from the group consisting of a ribonucleic acid and a deoxyribonucleic acid.

13. The composition of claim 1 wherein the therapeutic agent is selected from the group consisting of insulin, calcitonin, leuprolide and albuterol.

14. The composition of claim 1 wherein the surfactant is selected from the group consisting of a fatty acid, a phospholipid, and a poloxamer.

15. The composition of claim 1 wherein the surfactant is a phosphoglyceride.

16. The composition of claim 1 wherein the surfactant is dipalmitoyl L-.alpha.-phosphatidylcholine.

17. A method for drug delivery to the pulmonary system comprising:

administering to the respiratory tract of a patient in need of treatment an effective amount of biodegradable particles incorporating a therapeutic, prophylactic or diagnostic agent and a surfactant,

wherein the particles have a tap density less than about 0.4 g/cm.<sup>3</sup> and a mean diameter of between 5 .mu.m and 30 .mu.m effective to yield an aerodynamic diameter of the particles of between approximately one and three microns.

18. The method of claim 17 wherein at least 50% of the administered particles have a mean diameter between 5 .mu.m and 15 .mu.m.

19. The method of claim 18 wherein at least 50% of the administered particles have a mean diameter between 5 .mu.m and 15 .mu.m and a tap density of less than about 0.1 g/cm.<sup>3</sup>

20. The method of claim 17 wherein the particles comprise a biodegradable polymer.

21. The method of claim 17 wherein the particles comprise a polyester.

22. The method of claim 17 wherein the particles comprise an excipient.

23. The method of claim 21 wherein the particles have an irregular surface structure.

24. The method of claim 17 for delivery to the alveolar zone of the lung wherein at least 90% of the particles have a mean diameter between about 9 .mu.m and 11 .mu.m and a tap density less than 0.1 g/cm.sup.3.

25. The method of claim 17 wherein the therapeutic agent is selected from the group consisting of proteins, polysaccharides, lipids, nucleic acids and combinations thereof.

26. The method of claim 17 wherein the therapeutic agent selected from the group consisting of a ribonucleic acid and a deoxyribonucleic acid.

27. The method of claim 17 wherein the therapeutic agent is selected from the group consisting of insulin, calcitonin, leuprolide and albuterol.

28. The method of claim 17 wherein the particles are administered in combination with a pharmaceutically acceptable carrier for administration to the respiratory tract.

29. The method of claim 17 wherein the surfactant is selected from the group consisting of a fatty acid, a phospholipid, and a poloxamer.

30. The method of claim 17 wherein the surfactant is a phosphoglyceride.

31. The method of claim 17 wherein the surfactant is dipalmitoyl L-.alpha.-phosphatidylcholine.

32. The method of claim 17 wherein the surfactant is coated on the surface of the particle.

33. The method of claim 17 wherein the surfactant is incorporated within and on the surface of the particle.

[Previous Doc](#)

[Next Doc](#)

[Go to Doc#](#)

## Refine Search

### Search Results -

Terms	Documents
(pulmonary adj2 delivery) adj5 (microsphere or powder or microparticle)	80

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Set  
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Count Name  
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80 L1

END OF SEARCH HISTORY

[First Hit](#) [Fwd Refs](#)[Previous Doc](#) [Next Doc](#) [Go to Doc#](#) [Generate Collection](#) [Print](#)

L1: Entry 25 of 37

File: USPT

Nov 16, 1999

US-PAT-NO: 5985309

DOCUMENT-IDENTIFIER: US 5985309 A

**\*\* See image for Certificate of Correction \*\*****\*\* See image for Reexamination Certificate \*\***

TITLE: Preparation of particles for inhalation

DATE-ISSUED: November 16, 1999

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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Langer; Robert S.	Newton	MA		
Vanbever; Rita	Cambridge	MA		
Mintzes; Jeffrey	State College	PA		
Wang; Jue	State College	PA		
Chen; Donghao	State College	PA		

US-CL-CURRENT: 424/426; 424/43, 424/434, 424/45, 424/489, 424/501

## CLAIMS:

We claim:

1. Particles for drug delivery to the pulmonary system consisting of a therapeutic agent and a material selected from the group consisting of surfactant and a molecule having a charge opposite to the charge of the therapeutic agent and forming a complex thereto, wherein the particles have a tap density less than 0.4 g/cm.<sup>3</sup> and a mean diameter between 5 .mu.m and 30 .mu.m effective to yield an aerodynamic diameter of the particles of between approximately one and five microns.

2. The composition of claim 1 wherein the aerodynamic diameter of the particles is between approximately one and three microns.

3. The composition of claim 1 wherein at least 50% of the particles have a mean diameter between 5 .mu.m and 15 .mu.m and a tap density less than 0.1 g/cm.<sup>3</sup>

4. The composition of claim 1 further comprising a pharmaceutically acceptable carrier for administration to the lungs.

5. The composition of claim 1 wherein the particles comprise a complex of charged molecules and a surfactant.

6. The composition of claim 1 wherein the therapeutic agent is selected from

the group consisting of proteins, polysaccharides, lipids, nucleic acids and combinations thereof.

7. The composition of claim 1 wherein the therapeutic agent is selected from the group consisting of nucleotides and oligonucleotides.

8. The composition of claim 6 wherein the therapeutic agent is selected from the group consisting of insulin, calcitonin, leuprolide and albuterol.

9. The composition of claim 1 wherein the surfactant is selected from the group consisting of a fatty acid, a phospholipid, and a block copolymer.

10. The composition of claim 9 wherein the surfactant is a phosphoglyceride.

11. The composition of claim 9 wherein the surfactant is L-.alpha.-phosphatidylcholine dipalmitoyl.

12. The composition of claim 1 wherein the agent is a charged species and is present as a complex with an oppositely charged species.

13. The composition of claim 12 wherein the agent is hydrophilic and is present as a complex with a hydrophobic moiety.

14. A method for drug delivery to the pulmonary system comprising:

administering to the respiratory tract of a patient in need of treatment an effective amount of particles consisting of a therapeutic agent and a molecule selected from the group consisting of surfactant and a molecule having a charge opposite to the charge of the therapeutic agent and forming a complex thereto,

wherein the particles have a tap density less than about 0.4 g/cm.<sup>3</sup> and a mean diameter of between 5 .mu.m and 30 .mu.m effective to yield an aerodynamic diameter of the particles of between approximately one and five microns.

15. The method of claim 14 wherein the aerodynamic diameter of the particles is between approximately one and three microns.

16. The method of claim 14 wherein at least 50% of the administered particles have a mean diameter between 5 .mu.m and 15 .mu.m.

17. The method of claim 14 wherein at least 50% of the administered particles have a mean diameter between 5 .mu.m and 15 .mu.m and a tap density of less than about 0.1 g/cm.<sup>3</sup>.

18. The method of claim 14 wherein the particles comprise a complex of charged molecules and surfactant.

19. The method of claim 14 for delivery to the alveolar zone of the lung wherein at least 90% of the particles have a mean diameter between about 9 .mu.m and 11 .mu.m and a tap density less than 0.1 g/cm.<sup>3</sup>.

20. The method of claim 14 wherein the therapeutic agent is selected from the group consisting of proteins, polysaccharides, lipids, nucleic acids and combinations thereof.

21. The method of claim 14 wherein the therapeutic agent selected from the group consisting of nucleotides and oligonucleotides.
22. The method of claim 20 wherein the therapeutic agent is selected from the group consisting of insulin, calcitonin, leuprolide and albuterol.
23. The method of claim 14 wherein the surfactant is selected from the group consisting of a fatty acid, a phospholipid, and a block copolymer.
24. The method of claim 23 wherein the surfactant is a phosphoglyceride.
25. The method of claim 23 wherein the surfactant is L-.alpha.-phosphatidylcholine dipalmitoyl.
26. The method of claim 14 wherein the agent is a charged species and is present as a complex with an oppositely charged species.
27. The method of claim 14 wherein the agent is hydrophilic and is present as a complex with a hydrophobic moiety.

[Previous Doc](#)[Next Doc](#)[Go to Doc#](#)